

IN THE CLAIMS:

Please amend the claims as follows:

Please cancel claims 1-72, *i.e.*, all of the pending claims, and add the following new claims 73-105:

73-105 PENDING / 83-89 REJECTED
73-82 / 90-105 w/d

1.-72. (Cancelled)

73. (New) A method of assessing the effectiveness of non-nucleoside reverse transcriptase inhibitor ("NNRTI") antiretroviral therapy of an HIV-infected patient comprising evaluating whether a plasma sample collected from the HIV-infected patient contains a nucleic acid encoding HIV reverse transcriptase having a mutation at codon 236, wherein the presence of the mutation at codon 236 is correlated with decreased susceptibility to delavirdine and no significant change in nevirapine susceptibility.
74. (New) The method of Claim 1, wherein the mutation at codon 236 encodes leucine (L).
75. (New) The method of claim 1, further comprising evaluating whether the nucleic acid encoding HIV reverse transcriptase has an additional mutation(s) at codon 103, codon 181 or a combination thereof.
76. (New) The method of claim 75, wherein the mutation at codon 103 encodes an asparagine (N) and the mutation at codon 181 encodes cysteine (C).
77. (New) The method of claim 1, wherein the HIV-infected patient is being treated with an antiretroviral agent.
78. (New) A method of assessing the effectiveness of antiretroviral therapy of an HIV-infected patient comprising evaluating whether a plasma sample collected from the HIV-infected patient contains a nucleic acid encoding HIV reverse transcriptase having a mutation at codon 225, wherein the mutation at codon 225 correlates with an increase in delavirdine susceptibility and no significant change in nevirapine susceptibility.

Amend. same
P. 58 pp 1-58

03/12/1999

Express Mail No.: EV 456 933 066 US

79. (New) The method of claim 78, wherein the mutated codon 225 encodes histidine (H).
80. (New) The method of claim 78, wherein the HIV-infected patient is being treated with an antiretroviral agent.
81. (New) The method of claim 78, further comprising evaluating whether the nucleic acid encoding HIV reverse transcriptase has an additional mutation(s) at codon(s) 103, 181 or a combination thereof.
82. (New) The method of claim 81, wherein the mutated codon 103 encodes asparagine (N) and the mutated codon 181 encodes cysteine (C).

102 (H)

(83)

(New) A method of assessing the effectiveness of a NNRTI on an HIV-infected patient, comprising evaluating whether a plasma sample collected from the HIV-infected patient contains a nucleic acid that has a mutation at codon 190, wherein the presence of the mutation at codon 190 is correlated with increased susceptibility to delavirdine and decreased susceptibility to nevirapine and efavirenz.

112 P 2
N.A. RUCODER
HIV-1 RT

(DLV) ↑

(NVP) ↓

(EFV) ↓

(DLV)

(NVP)

(EFV)

102 (H)

(84)

(New) The method of claim 83, wherein the mutation at codon 190 encodes alanine (A) or serine (S).

G190S/A

102 (H)

(85)

(New) The method of claim 83, further comprising evaluating whether the nucleic acid encoding reverse transcriptase has an additional mutation(s) at codon 101, codon 103, or a combination thereof, wherein the presence of the additional mutation(s) in combination with the mutation at codon 190 is correlated with decreased susceptibility to delavirdine, nevirapine, and efavirenz.

K101E
K103N ✓

(86)

(New) The method of claim 85, wherein the mutation at codon 101 encodes glutamic acid (E) and the mutation at codon 103 encodes asparagine (N).

(87)

(New) The method of claim 83, wherein reverse transcriptase has an additional mutation at codon 98.

(88)

(New) The method of claim 87, wherein the mutation at codon 98 encodes glycine (G).

RESIST?

NONNUCLEOSIDE RT INHIBITOR

Amendment
CAJD: 505405.1

NNRTI

G190S, G190A, K101E, K103N

HUANG W

1998 FUSUWARA

TAMUR 5

1997
231(C):112
095
095
095

102(a)

(89)

(New) The method of claim 83, wherein the HIV-infected patient is being treated with an antiretroviral agent.

-
90. (New) A method of assessing the effectiveness of a NNRTI on an HIV-infected patient comprising evaluating whether a plasma sample collected from the HIV-infected patient contains a nucleic acid that has a mutation at codon 188, wherein the presence of the mutation at codon 188 is correlated with decreased susceptibility to delavirdine, nevirapine, and efavirenz.
91. (New) The method of claim 90, wherein the mutation at codon 188 encodes leucine (L), cysteine (C), or histidine (H).
92. (New) The method of claim 90, further comprising evaluating whether the nucleic acid encoding the reverse transcriptase has an additional mutation(s) at codon 100, codon 103, codon 138, or a combination thereof.
93. (New) The method of claim 92, wherein the mutation at codon 100 encodes isoleucine (I), codon 103 encodes asparagine (N), and codon 138 encodes alanine (A).
94. (New) The method of claim 90, wherein the HIV-infected patient is being treated with an antiretroviral agent.
95. (New) A method of assessing the effectiveness of a NNRTI on an HIV-infected patient comprising evaluating whether a plasma sample collected from the HIV-infected patient contains a nucleic acid that has a mutation at codon 108, wherein the presence of the mutation at codon 108 is correlated with decreased susceptibility to nevirapine, and no significant change in susceptibility to delavirdine or efavirenz.
96. (New) The method of claim 95, wherein the mutation at codon 108 encodes isoleucine (I).
97. (New) The method of claim 95, wherein the HIV-infected patient is being treated with an antiretroviral agent.
98. (New) A method of assessing the effectiveness of a NNRTI on an HIV-infected patient comprising evaluating whether a plasma sample collected from the HIV-

infected patient contains a nucleic acid that exhibits a mutation at codon 106, wherein the presence of the mutation at codon 106 is correlated with decreased susceptibility to delavirdine or nevirapine, and no significant change in susceptibility to efavirenz.

99. (New) The method of claim 98, wherein the mutation at codon 106 encodes alanine (A).
100. (New) The method of claim 98, wherein the reverse transcriptase has an additional mutation at codon 189.
101. (New) The method of claim 100, wherein the mutation at codon 189 encodes leucine (L).
102. (New) The method of claim 98, wherein the HIV-infected patient is being treated with an antiretroviral agent.
103. (New) A method of assessing the effectiveness of a NNRTI on an HIV-infected patient comprising evaluating whether a plasma sample collected from the HIV-infected patient contains a nucleic acid that exhibits mutations at codons 106 and 227, wherein the presence of the mutations at codons 106 and 227 is correlated with decreased susceptibility to delavirdine, nevirapine, and efavirenz.
104. (New) The method of claim 103, wherein the mutation at codon 106 encodes alanine (A) and the mutation at codon 227 encodes leucine (L).
105. (New) The method of claim 103, wherein the HIV-infected patient is being treated with an antiretroviral agent.

susceptibility. The presence of mutations at 100 and 103 correlates with a substantial decrease in delavirdine susceptibility, a moderate decrease in nevirapine susceptibility and a substantial decrease in efavirenz susceptibility. The presence of mutations at 103 and 100 and 188 correlates with a substantial decrease in delavirdine susceptibility, a substantial decrease in nevirapine susceptibility and a substantial decrease in efavirenz susceptibility. The mutations were found in plasma HIV RNA after a period of time following initiation of NNRTI therapy. The developemnt of the codon 103 and 100 and/or 188 mutations in HIV RT was found to be an indicator of the development of alterations in phenotypic susceptibility/resistance which has been associated with virologic failure and subsequent immunological decline.

In a further embodiment of the invention, PCR based assays, including phenotypic and genotypic assays, may be used to detect mutations at codon 225 in combination with mutations at other codons including 103 of HIV RT which correlate with a specific pattern of resistance to antiretroviral therapies and subsequent immunologic decline. In yet another embodiment of the invention, PCR based assays, including phenotypic and genotypic assays, may be used to detect mutations at codon 236 either alone or in combination with mutations at other codons including 103 and/or 181 of HIV RT which correlate with resistance to antiretroviral therapy and immunologic decline. In yet another embodiment of the invention, PCR based assays, including phenotypic and genotypic assays, may be used to detect mutations at codon 190 (G190S) either alone or in combination with mutation at codon 101 (K101E) of HIV RT which correlates with resistance to antiretroviral therapy and immunologic decline. In still another embodiment of the invention, PCR based assays, including phenotypic and genotypic assays, may be used to detect mutations at codon 190 (G190A) either alone or in combination with mutation at codon 103 (K103N) of HIV RT which correlates with